American Journal of Epidemiology
Vol. 162, No. 10
DOI: 10.1093/aje/kwi318

Human Genome Epidemiology (HuGE) Review

Genetic Polymorphisms in the Base Excision Repair Pathway and Cancer Risk: A HuGE Review

Rayjean J. Hung, Janet Hall, Paul Brennan, and Paolo Boffetta

From the Genetic Epidemiology Group, International Agency for Research on Cancer, Lyon, France.

Received for publication May 3, 2005; accepted for publication June 23, 2005.

Genetic variations in DNA repair genes are thought to modulate DNA repair capacity and are suggested to be related to cancer risk. However, epidemiologic findings have been inconsistent. The authors conducted meta-analyses of associations between genes in the base excision repair pathway and cancer risk, focusing on three key genes: 8-oxoguanine DNA glycosylase (*OGG1*), apurinic/apyrimidinic endonuclease (*APE1*/*APEX1*), and x-ray repair cross-complementing group 1 (*XRCC1*). They found increased lung cancer risk among subjects carrying the *OGG1* Cys/Cys genotype (odds ratio (OR) = 1.24, 95% confidence interval (CI): 1.01, 1.53), using 3,253 cases and 3,371 controls from seven studies; this is consistent with experimental evidence that this isoform exhibits decreased activity. They found a protective effect of the *XRCC1* 194Trp allele for tobacco-related cancers (OR = 0.86, 95% CI: 0.77, 0.95), using 4,895 cases and 5,977 controls from 16 studies; this is compatible with evidence of lower mutagen sensitivity for this allele. The *XRCC1* 399Gln/399Gln genotype was associated with increased risk of tobacco-related cancers among light smokers (OR = 1.38, 95% CI: 0.99, 1.94) but decreased risk among heavy smokers (OR = 0.71, 95% CI: 0.51, 0.99), suggesting effect modification by tobacco smoking. There was no association between cancer risk and the *APE1/APEX1* Asp148Glu and *XRCC1* Arg280His polymorphisms. Recommendations for future studies include pooling of individual data to facilitate evaluation of multigenic effects and detailed analysis of effect modification by environmental exposure.

apurinic/apyrimidinic endonuclease; DNA repair; meta-analysis; neoplasms; 8-oxoguanine DNA glycosylase, human; polymorphism, genetic; XRCC1 protein

Abbreviations: APE1/APEX1, apurinic/apyrimidinic endonuclease; CI, confidence interval; dbSNP, Database of Single Nucleotide Polymorphisms; OGG1, 8-oxoguanine DNA glycosylase; OR, odds ratio; XRCC1, x-ray repair cross-complementing group 1.

Editor's note: *This paper is also available on the website of the Human Genome Epidemiology Network (http://www.cdc.gov/genomics/hugenet/).*

There is growing evidence that genetic predisposition to cancer acts via a combination of high-risk variants in a set of low- and medium-penetrance genes rather than a few high-penetrance genes. Recent genetic association studies on cancer risk have focused on identifying effects of single nucleotide polymorphisms in candidate genes, among which DNA repair genes are increasingly studied because of their critical role in maintaining genome integrity. The base excision repair pathway is one DNA repair pathway which removes various forms of base damage via a number of coordinated sequential reactions that detect and process the damage (1). Mammalian cells contain 11 different glycosylases, each with a specialized function, as reviewed by Barnes and Lindahl (2). In the first step, a DNA glycosylase, such as

Correspondence to Dr. Rayjean J. Hung, Genetic Epidemiology Group, International Agency for Research on Cancer, 150 cours Albert-Thomas, 69008 Lyon, France (e-mail: hung@iarc.fr).

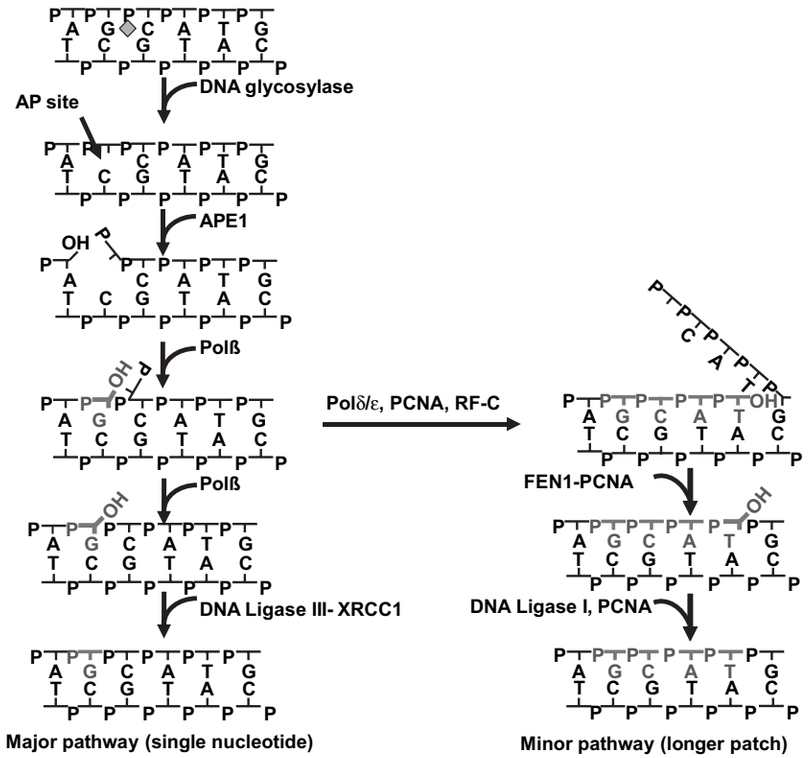

FIGURE 1. Diagram of the short-patch and long-patch base excision repair pathways. The damaged base (G♦) is recognized by a DNA glycosylase that hydrolytically cleaves the base-deoxyribose glycosyl bond of the damaged nucleotide residue, generating an apurinic/apyrimidinic (AP) site. The apurinic/apyrimidinic endonuclease (APE1) then cleaves the sugar-phosphate chain on the 5′ side of the abasic site and recruits polymerase β (Polβ), which adds one nucleotide to the 3′ end of the nick. In the major pathway, the 5′-teminal deoxyribose-phosphate residue is excised by the lyase activity of polymerase β. Polymerase β also interacts with x-ray repair cross-complementing group 1 (XRCC1) present in a heterodimer with DNA ligase III. Consequently, XRCC1 acts as a scaffold protein by bringing the polymerase and the ligase together at the site of repair. This XRCC1-ligase III heterodimer completes the repair process, generating a single nucleotide repair patch (short-patch base excision repair). In cases where the terminal sugar-phosphate residue has a more complex structure which is resistant to cleavage by the apurinic/apyrimidinic lyase activity of polymerase β, a few more nucleotides are added to the 3′ end by polymerase δ/ε (Polδ/ε), generating a flap containing the 5′-sugar phosphate. This switches the repair to the long-patch base excision repair subpathway, where the flap is removed by flap endonuclease 1 (FEN1), with proliferating cell nuclear antigen (PCNA) stimulating these reactions and acting as a scaffold protein in a manner similar to that of XRCC1 in the main pathway. DNA ligase I then completes this longer-patch form of repair. RF-C, replication factor C. (Modified from references 2, 4, and 12).

8-oxoguanine DNA glycosylase (OGG1), initiates this process by releasing the modified base, which generates an apurinic/apyrimidinic site. Some glycosylases (the bifunctional glycosylases) have an associated apurinic/apyrimidinic lyase activity and further catalyze the cleavage of the sugar-phosphate chain and excision of the abasic residue, leaving a single nucleotide gap. This gap is filled by DNA polymerase β, and the nick is sealed by the DNA ligase III/x-ray repair cross-complementing group 1 (XRCC1) complex. Certain glycosylases (the monofunctional DNA glycosylases) have no associated lyase activity. When such enzymes initiate repair, the phosphodiester bond at the 5′ side of the intact apurinic/apyrimidinic site is incised by apurinic/apyrimidinic endonuclease (APE1/APEX1). DNA polymerase β, DNA ligase III, and XRCC1 complete the repair process. The net result is the replacement of a single nucleotide; this is called short-patch base excision repair (1–5). A subpathway of base excision repair, the long-patch repair—which appears to play a crucial role in processing oxidized or reduced apurinic/apyrimidinic sites that are resistant to the apurinic/apyrimidinic lyase activity of DNA polymerase β—results in the replacement of several nucleotides (1–5). These pathways are illustrated in figure 1.

Sequence variants in DNA repair genes are thought to modulate DNA repair capacity and consequently are suggested to be associated with altered cancer risk (6). However, results from epidemiologic studies have been inconsistent, possibly because of 1) low statistical power for detecting a moderate effect, 2) false-positive results, 3) heterogeneity across study populations, 4) failure to consider effect modifiers such as environmental exposures, and 5) publication bias. Reliable knowledge of which sequence variants influence cancer risk may help in identifying persons at high risk of developing cancer and shed light on cancer etiology.

TABLE 1. Study characteristics and genotype prevalences from published studies on the relation of the 8-oxoguanine DNA glycosylase (*OGG1*) Ser326Cys polymorphism and the apurinic/apyrimidinic endonuclease (*APE1*/*APEX1*) Asp148Glu polymorphism to cancer risk

Cancer site or type	First author	Year	Ref. no.	Country	Ethnicity of subjects	No. of cases	No. of controls	Source of controls	Matching	Genotype 1/2 (heterozygotes)	Genotype 2/2 (rare-allele homozygotes)	Hardy-Weinberg *p* value*
					OGG1 Ser326Cys							
Lung	Sugimura	1999	50	Japan	Asian	241	197	Hospital	No	54.3	13.7	0.08
	Ito	2002	51	Japan	Asian	138	240	Hospital	No information available	49.2	22.5	0.84
	Sunaga	2002	52	Japan	Asian	198	152	Hospital	No	43.4	23.7	0.13
	Lan	2004	53	China	Asian	118	109	Population	Frequency	39.4	13.8	0.23
	Le Marchand	2002	54	Hawaii	Japanese, Caucasian, Hawaiian	298	405	Population	Frequency	43.2	13.1	0.35
	Park	2004	37	United States	Caucasian, UEM†	179	350	Screening	Individual	24.9	2.3	0.86
	Wikman	2000	55	Germany	Caucasian	105	105	Hospital	Frequency	41.0	1.9	0.07
	Hung	2005	56	Europe	Caucasian, UEM	2,155	2,163	Hospital	Frequency	33.1	3.7	0.22
Upper aerodigestive tract	Xing	2001	39	China	Asian	196	201	Hospital healthy	Frequency	52.7	13.4	0.15
	Cho	2003	57	Taiwan	Asian	333	283	Community	Frequency	45.6	38.2	0.48
	Hao	2004	58	China	Asian	419	480	Population	Frequency	45.0	16.5	0.24
	Elahi	2002	38	United States	Caucasian	167	331	Hospital healthy	Frequency	23.0	1.8	0.94
	Zhang	2004	59	United States	Caucasian, UEM	706	1,196	Hospital healthy	Frequency	32.4	5.8	0.06
Colon	Kim	2003	60	Korea	Asian	125	247	Hospital healthy	Frequency	53.0	25.9	0.32
Stomach	Takezaki	2002	26	China	Asian	101	198	Population	Frequency	60.6	24.2	<0.01
	Hanaoka	2001	25	Brazil	Asian	58	127	Hospital	Individual	44.1	21.3	0.25
	Hanaoka	2001	25	Brazil	Non-Japanese Brazilian	208	205	Hospital	Individual	36.1	3.9	0.44
Breast	Choi	2003	61	Korea, Japan	Asian	466	468	Hospital	No	52.1	24.1	0.36
	Vogel	2003	62	Denmark	Caucasian	425	434	Population	Individual	38.9	4.6	0.18
Sporadic prostate cancer	Xu	2002	63	United States	Caucasian	199	174	Hospital healthy	No	36.2	8.6	0.32
Hereditary prostate cancer	Xu	2002	63	United States	Caucasian	99	174	Hospital healthy	No	36.2	8.6	0.32
Basal cell	Vogel	2004	64	Denmark	Caucasian	319	319	Population	Individual	39.2	8.5	0.60
					APE1/*APEX1* Asp148Glu							
Lung	Ito	2004	65	Japan	Asian	178	449	Hospital	Frequency	50.3	14.3	0.25
	Misra	2003	66	Finland	Caucasian	310	302	Population	Individual	53.0	25.5	0.29
	Popanda	2004	67	Germany	Caucasian	459	457	Hospital	No	51.0	23.2	0.66
Upper aerodigestive tract	Hao	2004	58	China	Asian	409	478	Population	Frequency	49.0	19.9	0.86

* *p* value for Hardy-Weinberg equilibrium in the control group.

† UEM, unspecified ethnic minorities.

TABLE 2. Study characteristics and genotype prevalences from published studies on the relation of the x-ray repair cross-complementing group 1 (*XRCC1*) Arg194Trp and Arg280His polymorphisms to cancer risk

Cancer site or type	First author	Year	Ref. no.	Country	Ethnicity of subjects	No. of cases	No. of controls	Source of controls	Matching	Genotype 1/2 (heterozygotes)	Genotype 2/2 (rare-allele homozygotes)	Hardy-Weinberg *p* value*
					XRCC1 Arg194Trp							
Lung	Ratnasinghe	2001	68	China	Asian	108	216	Population	Individual	48.1	9.7	0.26
	Chen	2002	69	China	Asian	109	109	Population	Individual	36.7	4.6	0.69
	David-Beabes	2001	23	United States	African-American	154	243	Population	Frequency	14.8	0.8	0.76
	David-Beabes	2001	23	United States	Caucasian	180	461	Population	Frequency	11.7	0.0	0.18
	Hung	2005	56	Europe	Caucasian, UEM†	2,147	2,132	Hospital	Frequency	13.7	0.6	0.93
Upper aerodigestive tract	Lee	2001	70	Taiwan	Asian	105	264	Hospital	Frequency	45.5	7.2	0.17
	Xing	2002	71	China	Asian	433	524	Population	Frequency	43.5	7.1	0.16
	Yu	2004	41	China	Asian	135	152	Check up	Frequency	39.5	2.6	0.09
	Hao	2004	58	China	Asian	411	478	Population	Frequency	43.7	7.9	0.33
	Sturgis	1999	72	United States	Caucasian, UEM	203	424	Hospital	Frequency	14.4	0.0	0.11
	Olshan	2002	73	United States	Caucasian	98	161	Hospital	Frequency	16.1	0.0	0.27
	Varzim	2003	74	Portugal	Caucasian	88	178	Blood donor	No	10.1	0.0	0.48
Bladder	Stern	2001	28	United States	Caucasian, UEM	232	210	Hospital	Frequency	17.6	0.0	0.16
Colorectum	Abdel-Rahman	2000	75	Egypt	African	48	48	Friend	Individual	10.4	0.0	0.70
Stomach	Shen	2000	76	China	Asian	188	166	Population	Frequency	46.4	11.4	0.75
	Lee	2002	77	Korea	Asian	190	172	Hospital	Frequency	50.0	8.1	0.09
Prostate	van Gils	2002	78	United States	Caucasian, African-American	76	182	Population	Frequency	15.4	1.1	0.58
Breast	Duell	2001	24	United States	African-American	155	160	Population	Frequency	12.5	0.0	0.40
	Duell	2001	24	United States	Caucasian	233	221	Population	Frequency	13.1	0.9	0.45
	Han	2003	79	United States	Caucasian	998	1,369	Population	Frequency	12.9	0.2	0.18
	Smith	2003	80	United States	Caucasian	114	230	Clinic	No information available	15.7	0.4	0.62
	Smith	2003	81	United States	Caucasian	246	266	Hospital healthy	Frequency	8.6	0.4	0.57
	Moullan	2003	82	France	Caucasian	254	312	Blood donor	No	13.1	0.3	0.67
	Forsti	2004	83	Finland/Poland	Caucasian	223	298	Blood donor	Frequency	5.4	0.0	0.63
	Deligezer	2004	84	Turkey	Turkish	151	133	Healthy	No information available	10.5	0	0.52
	Kim	2002	32	Korea	Asian	205	205	Hospital	Individual	42.0	13.2	0.34
	Chacko	2005	40	India	Asian	123	123	Hospital	Individual	18.7	3.3	0.09
Acute myeloid leukemia	Seedhouse	2002	27	Finland	Caucasian	114	87	No information available	No	8.0	2.3	<0.01
Skin	Winsey	2000	31	United Kingdom	Caucasian	125	211	Hospital healthy	No	17.1	0.0	0.18

						XRCC1 Arg280His						
Lung	Ratnasinghe	2001	68	China	Asian	106	209	Population	Individual	15.3	0.0	0.23
	Misra	2003	66	Finland	Caucasian	309	302	Population	Individual	13.9	0.0	0.19
	Hung	2005	56	Europe	Caucasian, UEM	2,088	2,092	Hospital	Frequency	9.1	0.3	0.59
Upper aerodigestive tract	Lee	2001	70	Taiwan	Asian	105	264	Hospital	Frequency	18.9	0.8	0.61
	Cho	2003	57	Taiwan	Asian	332	283	Community	Frequency	23.3	0.7	0.20
	Hao	2004	58	China	Asian	415	480	Population	Frequency	20.0	0.4	0.12
Bladder	Stern	2001	28	United States	Caucasian, UEM	233	208	Hospital	Frequency	6.3	1.0	<0.01
Stomach	Lee	2002	77	Korea	Asian	190	172	Hospital	Frequency	20.3	0.0	0.14
Breast	Moullan	2003	82	France	Caucasian	254	312	Blood donor	No	9.3	0.0	0.39
	Chacko	2005	40	India	Asian	123	123	Hospital	Individual	26.0	1.6	0.65
Prostate	van Gils	2002	78	United States	Caucasian, African-American	76	182	Population	Frequency	9.9	0.0	0.48

* *p* value for Hardy-Weinberg equilibrium in the control group.
† UEM, unspecified ethnic minorities.

Therefore, we conducted a systematic Human Genome Epidemiology review on associations between genes in the base excision repair pathway and cancer risk, focusing on genes encoding three key enzymes in this repair pathway: OGG1, APE1/APEX1, and the XRCC1 protein.

GENES AND GENE VARIANTS

8-Oxoguanine DNA glycosylase

The *OGG1* gene is located on chromosome 3p26.2, a region that frequently shows loss of heterozygosity in several human cancers (7, 8). It consists of seven exons and six introns and encodes a 345 amino acid, a bifunctional glycosylase.

OGG1 repairs one of the most mutagenic lesions among base damages, 8-oxoguanine, also called 8-hydroxyguanine when present in DNA in its alternative tautomeric form. 8-Oxoguanine is able to base-pair with adenine and cause G:C→T:A transversions in repair-deficient bacteria and yeast (7). At least 20 validated sequence variants have been described to date in Internet databases. Among those, a C→G sequence variant leading to an amino acid change from serine to cysteine at codon 326 (Ser326Cys; Database of Single Nucleotide Polymorphisms (dbSNP) no. rs1052133) has been studied most frequently. Several in vivo or in vitro studies have examined the association between *OGG1* genotypes and enzyme activity, though the results have been inconsistent, as reviewed by Weiss et al. (9). Although no association was found between *OGG1* genotypes and the enzyme activity of OGG1 in two studies (10, 11), Kohno et al. (8) found, by using a complementation assay of an *Escherichia coli* mutant defective in the repair of 8-oxoguanine, that 326Ser-containing OGG1 has a sevenfold higher activity for repairing 8-oxoguanine than 326Cys-containing OGG1.

Apurinic/apyrimidinic endonuclease

The gene encoding APE1 (also known as APEX1, HAP1, or REF1) is located on chromosome 14q11.2–q12 and encodes a 317 amino acid protein. It processes the abasic sites left from the incision of the damaged base by cleaving the DNA backbone at the 5′ side to the abasic site, leaving a 3′-hydroxyl group and a 5′-deoxyribose phosphate group flanking the nucleotide gap (5, 12, 13). APE1 also processes other 3′ DNA termini that impede further gap filling or religation, allowing repair to be completed; thus, it is an essential protein playing a pivotal role in the processing of abasic sites. Attempts to create *Ape1*-null mice have demonstrated an early embryonic lethality. Several sequence variants were identified in this gene, including a G→T change in exon 5 leading to an amino acid change from aspartic acid to glutamic acid (Asp148Glu; dbSNP no. rs3136820), a C→G change in exon 3 leading to an amino acid change from glutamic acid to histidine (Gln51His; dbSNP no. rs1048945), and an A→G substitution resulting in an amino acid change from isoleucine to valine in exon 64 (Ile64Val; dbSNP no. rs2307486). While the impact of the Gln51His and Ile64Val variants on enzyme function

TABLE 3. Study characteristics and genotype prevalences from published studies on the relation of the x-ray repair cross-complementing group 1 (*XRCC1*) Arg399Gln polymorphism to cancer risk

Cancer site or type	First author	Year	Ref. no.	Country	Ethnicity of subjects	No. of cases	No. of controls	Source of controls	Matching	Genotype 1/2 (heterozygotes)	Genotype 2/2 (rare-allele homozygotes)	Hardy-Weinberg *p* value*
Lung	Ratnasinghe	2001	68	China	Asian	107	208	Population	Individual	38.5	5.3	0.57
	Chen	2002	69	China	Asian	109	109	Population	Individual	36.7	6.4	0.87
	Park	2002	85	Korea	Asian	192	135	Hospital healthy	Frequency	35.6	4.4	0.74
	Ito	2004	65	Japan	Asian	178	449	Hospital	Frequency	37.6	5.8	0.76
	Zhang	2005	86	China	Asian	1,000	1,000	Hospital	Frequency	38.0	8.9	0.08
	David-Beabes	2001	23	United States	African-American	154	243	Population	Frequency	28.8	3.7	0.65
	David-Beabes	2001	23	United States	Caucasian	180	461	Population	Frequency	47.1	12.6	0.67
	Divine	2001	87	United States	Caucasian, Hispanic	172	143	Hospital	No	44.8	9.8	0.76
	Zhou	2003	88	United States	Caucasian	1,091	1,240	Hospital healthy	No	44.0	11.5	0.66
	Harms	2004	89	United States	Caucasian	110	119	Cancer-free	Frequency	46.2	6.7	0.26
	Misra	2003	66	Finland	Caucasian	315	313	Population	Individual	41.5	9.3	0.84
	Popanda	2004	67	Germany	Caucasian	463	460	Hospital	No	48.3	14.6	0.71
	Hung	2005	56	Europe	Caucasian, UEM†	2,049	2,015	Hospital	Frequency	43.7	12.9	0.11
Upper aerodigestive tract	Lee	2001	70	Taiwan	Asian	105	264	Hospital healthy	Frequency	40.9	9.1	0.78
	Xing	2002	71	China	Asian	433	524	Population	Frequency	37.4	9.4	0.09
	Cho	2003	57	Taiwan	Asian	334	282	Community	Frequency	38.7	7.4	0.81
	Yu	2004	41	China	Asian	135	152	Check up	Frequency	38.8	3.3	0.19
	Hao	2004	58	China	Asian	411	479	Population	Frequency	41.1	6.9	0.48
	Sturgis	1999	72	United States	Caucasian, UEM	203	424	Hospital	Frequency	46.5	10.8	0.48
	Olshan	2002	73	United States	Caucasian	98	161	Hospital	Frequency	50.9	10.6	0.18
	Varzim	2003	74	Portugal	Caucasian	88	178	Hospital healthy	No	44.9	10.1	0.76
Bladder	Stern	2001	28	United States	Caucasian, UEM	233	210	Hospital	Frequency	45.7	12.4	0.98
	Kelsey	2004	29	United States	Caucasian, UEM	355	544	Population	Frequency	42.3	15.8	0.03
	Matullo	2001	42	Italy	Caucasian	124	84	Hospital	No	48.8	14.3	0.79
	Shen	2003	90	Italy	Caucasian	201	214	Hospital	Frequency	45.8	11.2	0.78
	Sanyal	2004	91	Sweden	Caucasian	311	246	No information available	Frequency	44.7	9.3	0.61
Colorectum	Abdel-Rahman	2000	75	Egypt	African	48	48	Friend	Individual	18.8	4.1	0.17
	Yeh	2005	92	Taiwan	Asian	776	736	Hospital	Frequency	39.5	7.3	0.99
Stomach	Shen	2000	76	China	Asian	188	166	Population	Frequency	35.5	7.8	0.39
	Lee	2002	77	Korea	Asian	190	172	Hospital	Frequency	34.3	5.2	0.87
Liver	Yu	2003	93	Taiwan	Asian	577	389	Hospital	Frequency	36.8	7.2	0.50
Pancreas	Duell	2002	30	United States	Caucasian, UEM	293	919	Population	Frequency	39.7	11.1	0.03
Breast	Duell	2001	24	United States	African-American	253	266	Population	Frequency	24.1	1.5	0.65
	Duell	2001	24	United States	Caucasian	386	381	Population	Frequency	41.5	15.5	0.05
	Han	2003	79	United States	Caucasian	986	1,337	Population	Frequency	46.1	13.2	0.93

	Smith	2003	80	United States	Caucasian	114	229	Hospital	No information available	52.0	10.5	0.07
	Smith	2003	81	United States	Caucasian	251	267	Hospital healthy	Frequency	46.1	10.9	0.65
	Moullan	2003	82	France	Caucasian	254	312	Blood donor	No	46.8	12.5	0.77
	Forsti	2004	83	Finland/Poland	Caucasian	223	298	Blood donor	Frequency	43.3	10.4	0.92
	Kim	2002	32	Korea	Asian	205	205	Hospital	Individual	49.3	6.8	0.04
	Shu	2003	33	China	Asian	1,088	1,182	Population	Frequency	42.1	6.3	0.04
	Deligezer	2004	84	Turkey	Turkish	151	133	Healthy	No information available	49.6	12.8	0.51
	Chacko	2005	40	India	Asian	123	123	Hospital	Individual	28.5	7.3	0.08
Prostate	van Gils	2002	78	United States	Caucasian, African-American	76	182	Population	Frequency	42.9	14.8	0.33
	Rybicki	2004	94	United States	Caucasian, UEM	637	480	Brothers	Sibling	43.3	11.7	0.58
Acute myeloid leukemia	Seedhouse	2002	27	Finland	Caucasian	178	178	No information available	No	42.7	26.4	0.05
Lymphoma	Matsuo	2004	95	Japan	Asian	260	500	Hospital healthy	No	36.6	6.0	0.91
Skin	Winsey	2000	31	United Kingdom	Caucasian	125	211	Hospital healthy	No	55.0	9.5	0.01
	Nelson	2002	96	United States	Caucasian	745	431	Population	Frequency	42.9	16.5	0.07
	Yin	2002	97	United States	Caucasian	97	63	Hospital	Frequency	39.7	14.3	0.35

* *p* value for Hardy-Weinberg equilibrium in the control group.
† UEM, unspecified ethnic minorities.

has not yet been elucidated, it has been suggested that Asp148Glu may be associated with hypersensitivity to ionizing radiation (14).

X-ray repair cross-complementing group 1

The XRCC1 protein is essential for mammalian viability. *XRCC1* deficiency in mice results in embryonic lethality, and XRCC1 is required for the efficient repair of single-strand breaks and damaged bases in DNA. XRCC1 has no known enzymatic activity, and it is thought to act as a scaffold protein for both single-strand break repair and base excision repair activities (4). XRCC1 has been shown to physically interact with DNA polymerase β, polyadenosine diphosphate-ribose polymerases 1 and 2, APE1/APEX1, OGG1, and proliferating cell nuclear antigen. Its absence leads to a substantial reduction in the levels of its partner ligase III (15–17). The gene is located on chromosome 19q13.2; it consists of 17 exons and encodes a protein of 633 amino acids (4). More than 60 validated single nucleotide polymorphisms in *XRCC1* are listed in the Ensembl database, among which approximately 30 variants are located in exons or promoter regions. The most extensively studied single nucleotide polymorphisms are Arg194Trp on exon 6 (dbSNP no. rs1799782), Arg280His on exon 9 (dbSNP no. rs25489), and Arg399Gln on exon 10 (dbSNP no. rs25487). The Arg194Trp variant has been shown to be associated with lower bleomycin and benzo(*a*)pyrene diol epoxide sensitivity in vitro (18). The functional significance of Arg280His is not yet well-established; however, the 280His is located in the proliferating cell nuclear antigen-binding region and was suggested in a small study ($n = 80$) to be associated with higher bleomycin sensitivity (16, 19). The 399Gln allele is located at the carboxylic acid terminal side of the polyadenosine diphosphate-ribose polymerase-interacting domain. It was shown to be associated with higher levels of aflatoxin B_1-DNA adducts and higher bleomycin sensitivity in several studies (18, 20, 21), while another study did not find such an association (22).

Reliable knowledge on which base excision repair sequence variants are associated with cancer risk would help to elucidate the disease mechanism. Given that most of the previous studies had inadequate statistical power, we have conducted a systematic review on sequence variants in these three key players in this repair pathway.

Prevalence of gene variants

To estimate the prevalence of *XRCC1, OGG1*, and *APE1/APEX1* variants and their associated cancer risk, we conducted MEDLINE searches for case-control studies published up to February 1, 2005, on the associations between these genes and cancer risk. When more than one article was identified for the same study population, we included the most recent publication. When one publication reported results from more than one population, with an indication that different populations were recruited separately, we considered them to be separate study populations (23–25). Cancers studied included lung, upper aerodigestive tract (*International Classification of Diseases for Oncology* codes

TABLE 4. Summary odds ratios for the relation of the 8-oxoguanine DNA glycosylase (*OGG1*) Ser326Cys polymorphism to cancer risk

Stratifying factor and genotype	No. of studies*	Odds ratio	95% confidence interval	Heterogeneity *p* value	Egger's test *p* value
Cancer site or type					
Lung†					
Ser/Cys	7	0.99	0.81, 1.22	0.06	0.39
Cys/Cys	7	1.24	1.01, 1.53	0.38	0.71
Cys/Cys vs. others	7	1.23	0.96, 1.57	0.14	0.72
Upper aerodigestive tract‡					
Ser/Cys	3	1.09	0.82, 1.45	0.08	0.20
Cys/Cys	3	1.15	0.90, 1.46	0.47	0.56
Cys/Cys vs. others	3	1.02	0.83, 1.25	0.62	0.95
Stomach					
Ser/Cys	3	0.88	0.68, 1.14	0.59	0.81
Cys/Cys	3	0.75	0.47, 1.17	0.80	0.18
Cys/Cys vs. others	3	0.79	0.53, 1.16	0.78	0.62
Tobacco-related cancers§					
Ser/Cys	13	0.99	0.87, 1.12	0.08	0.20
Cys/Cys	13	1.14	0.99, 1.33	0.41	0.65
Cys/Cys vs. others	13	1.09	0.93, 1.27	0.18	0.95
Tobacco smoking§,¶					
Never smokers					
Ser/Cys	3	1.23	0.86, 1.74	0.30	0.25
Cys/Cys	3	1.14	0.58, 2.22	0.14	0.23
Cys/Cys vs. others#	3	0.67	0.41, 1.09	0.37	0.86
Ever smokers					
Ser/Cys	3	0.88	0.76, 1.01	0.71	0.78
Cys/Cys	3	1.11	0.81, 1.52	0.62	0.29
Cys/Cys vs. others	4	1.06	0.81, 1.40	0.54	0.08
Interaction odds ratio (case-case)					
Ser/Cys	3	0.85	0.64, 1.14	0.58	0.75
Cys/Cys	3	0.83	0.37, 1.84	0.06	0.08
Cys/Cys vs. others#	3	1.32	0.80, 2.21	0.51	0.21

* The number of studies may differ in each stratum, depending on the amount of information provided in the published articles.

† The study by Park et al. (37) (the study contributing the most heterogeneity) was excluded.

‡ The study by Elahi et al. (38) (the study with the largest variance) was excluded because of publication bias (Egger's test: $p = 0.03$). The study by Xing et al. (39) (the study contributing the most heterogeneity) was excluded because of high heterogeneity ($p < 0.01$).

§ Tobacco-related cancers included cancers of the lung, upper aerodigestive tract, bladder, stomach, liver, and pancreas, as well as myeloid leukemia (34). The studies by Park et al. (37), Elahi et al. (38), and Xing et al. (39) were excluded.

¶ Tobacco-related cancers only.

The study by Hung et al. (56) was further excluded because of high heterogeneity.

140–150 and 161), colorectal, bladder, liver, pancreas, prostate, breast, skin, and hematologic malignancies.

For each publication, we extracted information on the publication year, cancer site, control source, country, numbers of cases and controls, matching type and factors, ethnic composition of the population, and genotype frequency for the reported locus. We assessed departure from Hardy-Weinberg equilibrium for the control group in each study. Characteristics of individual studies are summarized in tables 1–3, presented by gene and type of cancer. In total, 22 studies were included for *OGG1* Ser326Cys, four studies for *APE1/APEX1* Asp148Glu, 29 studies for *XRCC1* Arg194Trp, 11 studies for *XRCC1* Arg280His, and 50 studies for *XRCC1* Arg399Gln.

TABLE 5. Summary odds ratios for the relation of the x-ray repair cross-complementing group 1 (*XRCC1*) Arg194Trp polymorphism to cancer risk

Stratifying factor and genotype	No. of studies*	Odds ratio	95% confidence interval	Heterogeneity *p* value	Egger's test *p* value
Cancer site or type					
Lung					
Arg/Trp	5	0.85	0.64, 1.12	0.12	0.98
Trp/Trp	4	1.05	0.58, 1.91	0.28	0.31
Arg/Trp or Trp/Trp	5	0.86	0.65, 1.13	0.09	0.97
Upper aerodigestive tract					
Arg/Trp	7	0.87	0.74, 1.02	1.00	0.86
Trp/Trp	4	1.26	0.78, 2.06	0.13	0.31
Arg/Trp or Trp/Trp	7	0.93	0.81, 1.08	0.96	0.29
Tobacco-related cancers†					
Arg/Trp	16	0.83	0.75, 0.92	0.65	0.37
Trp/Trp	10	1.05	0.75, 1.47	0.09	0.28
Arg/Trp or Trp/Trp	16	0.86	0.77, 0.95	0.40	0.44
Breast‡					
Arg/Trp	9	0.94	0.77, 1.15	0.22	0.87
Trp/Trp	5	1.07	0.64, 1.84	0.69	0.13
Arg/Trp or Trp/Trp	9	0.95	0.78, 1.16	0.20	0.79
Tobacco smoking (Arg/Trp or Trp/Trp)§					
Never	5	1.01	0.68, 1.50	0.52	0.73
Ever	5	0.77	0.58, 1.01	0.20	0.48
Light¶	4	0.76	0.43, 1.33	0.07	0.99
Heavy¶	4	0.71	0.46, 1.10	0.21	0.49
Interaction odds ratio (case-case)	5	0.80	0.56, 1.16	0.38	0.96
Age of onset (Arg/Trp or Trp/Trp)					
Young¶	3	0.74	0.28, 1.92	0.10	0.97
Old¶	3	0.92	0.77, 1.11	0.60	0.47

* The number of studies may differ in each stratum, depending on the amount of information provided in the published articles.

† Tobacco-related cancers included cancers of the lung, upper aerodigestive tract, bladder, stomach, liver, and pancreas, as well as myeloid leukemia (34).

‡ The study by Chacko et al. (40) (the study contributing the most heterogeneity) was excluded.

§ Tobacco-related cancers only.

¶ Defined differently in different studies.

The *OGG1* Ser326Cys polymorphism is slightly more prevalent among Asians (39.4–60.6 percent carry the heterozygous variant; 13.4–38.2 percent carry the homozygous variant) than among persons of European descent (hereafter called Caucasians) (23.0–41.0 percent heterozygotes, 1.8–8.6 percent homozygotes). The genotype distributions in the control groups were under Hardy-Weinberg equilibrium in all studies, except for one Chinese study (26). The prevalences of *APE1/APEX1* Asp148Glu heterozygosity and homozygosity ranged from 49 percent to 53 percent and from 14.3 percent to 25.5 percent, respectively. The *XRCC1* Arg194Trp polymorphism also appeared to be more prevalent among Asians (18.7–50.0 percent carried the heterozygous variant and 2.6–13.2 percent the homozygous variant) than among Caucasians (5.4–17.6 percent heterozygous, $\leq$2.3 percent homozygous). The genotype distributions in the control groups were under Hardy-Weinberg equilibrium in all studies, except for one small study conducted in Finland (27). The genotype frequency of Arg280His was 6.3–26.0 percent for the heterozygous variant and $\leq$1.6 percent for the homozygous variant, with no apparent ethnic differences. The genotype distributions in the control groups were under Hardy-Weinberg equilibrium in all studies, except for one bladder cancer study conducted in the United States (28). *XRCC1* Arg399Gln was the most common sequence variant among the three *XRCC1* polymorphisms studied, and there was no major variation by ethnicity. Genotype distributions in the control groups were not under

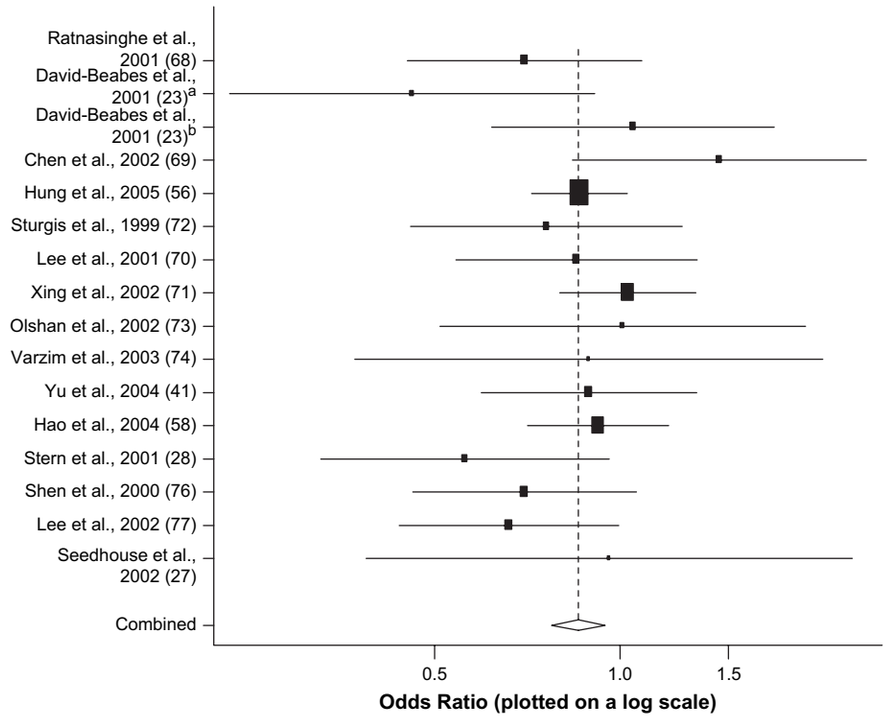

FIGURE 2. Odds ratios for the relation between the x-ray repair cross-complementing group 1 (*XRCC1*) Arg194Trp polymorphism (Arg/Trp and Trp/Trp vs. Arg/Arg) and risk of tobacco-related cancer among all subjects. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the variance of the estimated effect. Diamond, summary odds ratio; horizontal lines, 95% confidence interval. Reference (23)[a] corresponds to the African-American component in the study by David-Beabes et al. (23); reference (23)[b] corresponds to the Caucasian component.

Hardy-Weinberg equilibrium in several studies, including three US studies (24, 29, 30), one United Kingdom study (31), and two Asian studies (32, 33).

ASSOCIATIONS AND INTERACTIONS

To estimate the association between the base excision repair genetic variants and cancer risk, we conducted a meta-analysis of identified studies. We calculated the crude odds ratio and 95 percent confidence interval for each study whenever possible. The meta-analysis was performed on crude odds ratios, since the adjusted odds ratios were not comparable because of different covariates' being included in the multivariate regression models. Using persons with the homozygous common allele as the reference group, we calculated odds ratios for persons with the heterozygous and homozygous variants separately whenever possible (information available in at least three studies). Summary odds ratios were calculated for each cancer site separately and for tobacco-related cancers combined. Tobacco-related cancers included cancers of the lung, upper aerodigestive tract, bladder, stomach, liver, and pancreas, as well as myeloid leukemia (34). We aimed to investigate the effect modifications of tobacco exposures and age of onset. When the published

TABLE 6. Summary odds ratios for the relation of the x-ray repair cross-complementing group 1 (*XRCC1*) Arg280His polymorphism (Arg/His or His/His) to cancer risk

Cancer site or type	No. of studies	Odds ratio	95% confidence interval	Heterogeneity *p* value	Egger's test *p* value
Lung	3	1.10	0.84, 1.43	0.22	0.13
Upper aerodigestive tract	3	0.87	0.59, 1.28	0.07	0.43
Tobacco-related cancers*	8	1.03	0.84, 1.26	0.07	0.22

* Tobacco-related cancers included cancers of the lung, upper aerodigestive tract, bladder, stomach, liver, and pancreas, as well as myeloid leukemia (34).

data permitted, odds ratios were calculated for various categories of smoking (never, ever, former, current, light, and heavy smoking; defined differently in different studies) and different ages of onset (young and old persons; defined differently in different studies). Effect modification of tobacco smoking was evaluated for tobacco-related cancers only. Interaction odds ratios for smoking and age of onset were calculated using the case-only design.

The summary odds ratios were estimated using the random-effect model, which takes into account the heterogeneity among studies by adding a term to the model (35). We estimated the summary odds ratio when there were data from at least three studies available. The number of studies may appear to be different in each stratum, depending on the amount of information provided in the published articles. A test of heterogeneity was performed for each summary estimate. We evaluated publication bias by means of funnel plots and Egger's test (36).

We conducted influence analysis when there was evidence of heterogeneity or publication bias. When the study-specific odds ratios appeared to be heterogeneous, we evaluated the source of heterogeneity by Galbraith plot and by comparing the Q values. Studies contributing the most heterogeneity were excluded until the heterogeneity was reduced to a nonsignificant level. When there was evidence of publication bias, we excluded the studies that had the largest variance (from the right-hand side of the funnel plot) until the publication bias was reduced to a nonsignificant level. When a study was excluded from the calculation of summary odds ratios by cancer site, because of either its contribution to heterogeneity or publication bias, it was subsequently excluded from all relevant stratified analyses. All statistical analyses were conducted with Stata software, version 8 (Stata Corporation, College Station, Texas).

The individual odds ratios from each study for *OGG1* Ser326Cys are shown in Web table 1 (posted on the *Journal*'s website (www.aje.oxfordjournals.org)), and the summary odds ratios are shown in table 4. Combining data from all eight studies on lung cancer, the summary odds ratios were 1.09 (95 percent confidence interval (CI): 0.86, 1.40) for Ser/Cys carriers and 1.37 (95 percent CI: 1.02, 1.82) for Cys/Cys carriers (data not shown). However, there was evidence of heterogeneity between individual studies ($p < 0.01$ for Ser/Cys). One outlying study was identified as contributing the most heterogeneity (37). After removing this study, we still observed an increased risk of lung cancer for Cys/Cys carriers, finding an odds ratio of 1.24 (95 percent CI: 1.01, 1.53) based on 3,253 cases and 3,371 controls (table 4). Combing five studies of upper aerodigestive tract cancers, we observed an odds ratio of 1.28 (95 percent CI: 0.96, 1.69) for Cys/Cys carriers; however, the results of Egger's test suggested the presence of publication bias ($p = 0.03$), with the more imprecise studies reporting a positive effect. After exclusion of the study with the largest variance (38) and an outlying study (39) (heterogeneity $p < 0.01$), the odds ratio for Cys/Cys was reduced to 1.15 (95 percent CI: 0.90, 1.46) (table 4). Given the ethnic differences in the allele frequency of this sequence variant, we evaluated the effect of the 326Cys allele in Asian and Caucasian populations separately (data not shown). However, we did not observe a difference: The summary odds ratio was 1.16 (95 percent CI: 0.98, 1.40) for Asian populations and 1.15 (95 percent CI: 0.90, 1.46) for Caucasian populations. On the basis of limited data, we did not observe effect modification by smoking.

Web table 2 shows the individual and summary odds ratios for *APE1/APEX1* Asp148Glu. On the basis of 1,359 cases and 1,686 controls, we did not observe an association between the 148Glu allele and aerodigestive tract cancer. When we analyzed lung cancer separately, the summary odds ratio was 0.94 (95 percent CI: 0.77, 1.14; p for heterogeneity $= 0.56$; p for Egger's test $= 0.08$).

Web table 3 shows the odds ratios from individual studies for the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphisms. Table 5 shows the summary odds ratios for the *XRCC1* Arg194Trp polymorphism by cancer site, tobacco smoking, and age of onset. We did not observe an association between the 194Trp allele and the risk of lung or upper aerodigestive tract cancers. However, when we combined data from 16 studies on tobacco-related cancers (4,895 cases and 5,977 controls), the 194Trp allele was associated with a decreased risk of tobacco-related cancers (odds ratio (OR) = 0.86, 95 percent CI: 0.77, 0.95) (figure 2). There were 10 case-control studies on breast cancer and the *XRCC1* Arg194Trp polymorphism. The study-specific odds ratios for the Arg/Trp and Trp/Trp genotypes appeared to be heterogeneous ($p = 0.04$), mainly because of one outlying study (40). After removal of this study, the summary odds ratio for breast cancer was 0.95 (95 percent CI: 0.78, 1.16; p for heterogeneity $= 0.20$) (table 5). When data were stratified by smoking status for tobacco-related cancers, there seemed to be a small protective effect among ever smokers (OR = 0.77, 95 percent CI: 0.58, 1.01). Given the ethnic difference in the allele frequencies, we also analyzed Asian and Caucasian populations separately (data not shown). However, the effect was not modified by ethnicity: The summary odds ratio for having at least one 194Trp allele was 0.90 (95 percent CI: 0.78, 1.03) from nine studies conducted in Asian populations and 0.89 (95 percent CI: 0.80, 1.00) from 15 studies conducted in Caucasian populations.

Summary odds ratios for *XRCC1* Arg280His are shown in table 6. We did not observe an association between the 280His allele and either lung cancer, upper aerodigestive tract cancer, or tobacco-related cancers combined.

Summary odds ratios for *XRCC1* Arg399Gln, stratified by cancer site, tobacco smoking, and age of onset, are shown in table 7. On the basis of 6,120 lung cancer cases and 6,895 controls from 13 studies, we did not observe an association between the 399Gln allele and lung cancer risk. We identified eight studies on upper aerodigestive tract cancers. The study-specific odds ratios for the Gln/Gln genotype from these eight studies appeared to be heterogeneous ($p = 0.01$), mainly because of one outlying study (41). After excluding this outlying study, we observed a nonsignificant decreased risk of upper aerodigestive tract cancer among carriers of the 399Gln allele (OR = 0.88, 95 percent CI: 0.78, 1.01) (table 7). We identified a total of five studies on bladder cancer and the Arg399Gln polymorphism. There was evidence of publication bias in the summary odds ratio for bladder cancer for carriers of the Arg/Gln genotype

TABLE 7. Summary odds ratios for the relation of the x-ray repair cross-complementing group 1 (*XRCC1*) Arg399Gln polymorphism to cancer risk

Stratifying factor and genotype	No. of studies*	Odds ratio	95% confidence interval	Heterogeneity *p* value	Egger's test *p* value
Cancer site or type					
Lung					
Arg/Gln	13	1.01	0.93, 1.09	0.60	0.13
Gln/Gln	13	1.07	0.93, 1.23	0.33	0.90
Arg/Gln or Gln/Gln	13	1.02	0.96, 1.10	0.58	0.17
Upper aerodigestive tract†					
Arg/Gln	7	0.85	0.75, 0.98	0.69	0.84
Gln/Gln	7	1.00	0.74, 1.35	0.15	0.23
Arg/Gln or Gln/Gln	7	0.88	0.78, 1.01	0.56	0.69
Bladder‡					
Arg/Gln	4	1.19	0.98, 1.45	0.31	0.10
Gln/Gln	4	0.85	0.64, 1.13	0.49	0.57
Arg/Gln or Gln/Gln	4	1.12	0.95, 1.33	0.46	0.26
Tobacco-related cancers§					
Arg/Gln	29	1.00	0.94, 1.07	0.28	0.24
Gln/Gln	29	1.06	0.95, 1.18	0.25	0.48
Arg/Gln or Gln/Gln	29	1.02	0.96, 1.08	0.38	0.23
Breast					
Arg/Gln	11	1.06	0.94, 1.20	0.10	0.48
Gln/Gln	11	1.17	0.98, 1.39	0.25	0.14
Arg/Gln or Gln/Gln	11	1.07	0.96, 1.20	0.15	0.30
Skin					
Arg/Gln	3	0.94	0.75, 1.16	0.66	0.20
Gln/Gln	3	1.04	0.52, 2.05	0.05	0.25
Arg/Gln or Gln/Gln	3	0.90	0.74, 1.10	1.00	0.67
Tobacco smoking§,¶					
Never					
Arg/Gln	7	1.09	0.86, 1.40	0.84	0.90
Gln/Gln	5	1.23	0.70, 2.15	0.09	0.80
Arg/Gln or Gln/Gln	9	1.06	0.85, 1.31	0.74	0.74

Table continues

(Egger's test: $p = 0.04$). After exclusion of the study with the largest variance (42), the p value from Egger's test was increased to 0.10, and the summary odds ratio was 1.12 (95 percent CI: 0.95, 1.33) for carriers of the Arg/Gln or Gln/Gln genotype. Combining data from 11 studies on breast cancer, we did not observe an association between the presence of the 399Gln allele and risk of breast cancer; neither did we find an association between the 399Gln allele and risk of skin cancer from three studies on skin cancer.

When data were stratified by tobacco smoking for tobacco-related cancers, the presence of the 399Gln allele seemed to be associated with an increased risk of tobacco-related cancers among light smokers (OR = 1.20, 95 percent CI: 1.03, 1.40) (figure 3), whereas it was associated with a decreased risk among heavy smokers (OR = 0.81, 95 percent CI: 0.64, 1.04) (figure 4), with the effect being more prominent among carriers of the Gln/Gln genotype (OR = 0.71, 95 percent CI: 0.51, 0.99) (table 7). The interaction odds ratio from case-case analysis was 0.73 (95 percent CI: 0.51, 1.04) for the Gln/Gln genotype, which suggests an interaction less than multiplicativity between the Gln/Gln genotype and heavy tobacco smoking. We did not observe effect modification by age of onset.

DISCUSSION

We conducted a systematic literature review to evaluate the associations between sequence variants in three base excision repair genes and cancer risks. We also evaluated possible effect modifications by tobacco smoking and age of onset. In summary, we found an increased risk of lung cancer among subjects carrying the *OGG1* Cys/Cys genotype,

TABLE 7. Continued

Stratifying factor and genotype	No. of studies*	Odds ratio	95% confidence interval	Heterogeneity *p* value	Egger's test *p* value
Ever					
Arg/Gln	7	1.06	0.95, 1.19	0.34	0.55
Gln/Gln	7	0.95	0.79, 1.15	0.32	0.06
Arg/Gln or Gln/Gln	9	1.04	0.94, 1.16	0.30	0.18
Light#					
Arg/Gln	7	1.27	1.06, 1.51	0.74	0.70
Gln/Gln	6	1.38	0.99, 1.94	0.35	0.27
Arg/Gln or Gln/Gln	8	1.20	1.03, 1.40	0.77	0.54
Heavy#					
Arg/Gln	7	0.85	0.67, 1.09	0.12	0.42
Gln/Gln	7	0.71	0.51, 0.99	0.26	0.20
Arg/Gln or Gln/Gln**	7	0.81	0.64, 1.04	0.09	0.32
Interaction (case-case)					
Arg/Gln	7	0.99	0.79, 1.25	0.76	0.40
Gln/Gln	5	0.73	0.51, 1.04	0.37	0.12
Arg/Gln or Gln/Gln	9	0.97	0.79, 1.19	0.73	0.48
Age of onset (Arg/Gln or Gln/Gln)					
Young#,††	3	1.15	0.90, 1.45	0.18	0.58
Old#	4	1.05	0.95, 1.18	0.41	0.89

* The number of studies may differ in each stratum, depending on the amount of information provided in the published articles.

† The study by Yu et al. (41) (the study contributing the most heterogeneity) was excluded.

‡ The study by Matullo et al. (42) (the study with the largest variance) was excluded.

§ Tobacco-related cancers included cancers of the lung, upper aerodigestive tract, bladder, stomach, liver, and pancreas, as well as myeloid leukemia (34). The studies by Yu et al. (41) and Matullo et al. (42) were excluded.

¶ Tobacco-related cancers only.

Defined differently in different studies.

** The study by Duell et al. (30) (the study contributing the most heterogeneity) was further excluded because of high heterogeneity ($p = 0.01$).

†† The study by Abdel-Rahman et al. (75) (the study contributing the most heterogeneity) was excluded because of high heterogeneity ($p < 0.01$).

which is consistent with experimental evidence that this isoform exhibits decreased base excision repair activity (8, 43). Epidemiologic studies on the *OGG1* Ser326Cys polymorphism were reviewed previously; however, no meta-analysis was conducted (9). We also found a protective effect of the *XRCC1* 194Trp allele for tobacco-related cancers, which is compatible with the evidence of lower mutagen sensitivity for this allele (18). However, the effect of *XRCC1* 194Trp alleles was mainly observed in heterozygotes but not in homozygotes; therefore, the results should be treated with caution. We did not find an association between cancer risk and *APE1/APEX1* Asp148Glu or *XRCC1* Arg280His.

We observed modification of the effect of the *XRCC1* 399Gln/399Gln genotype by tobacco smoking. Studies showed that the 399Gln allele may be associated with higher mutagen sensitivity and higher levels of DNA adducts (18, 21). An increased risk of tobacco-related cancers among light smokers who carried the Gln/Gln genotype is consistent with the functional data. Conversely, the mechanistic basis of a decreased risk among heavy smokers who carried the Gln/Gln genotype remains to be elucidated. Compatible with our findings, Matullo et al. (21) reported that Gln/Gln carriers had higher DNA adduct levels than Arg/Arg carriers among never smokers but lower DNA adduct levels among current smokers, though the differences were not statistically significant. It is possible that the resulting increased levels of DNA damage from heavy tobacco smoking might give rise to enhanced apoptosis at the time of cell division and would be manifested as a reduced risk of exposure-induced cancer. Such a model has been proposed to explain reduced risks of sunburn-related nonmelanoma skin cancer in homozygotic carriers of the *XRCC1* codon 399 glutamine variant (44). Alternatively, tobacco smoking might induce DNA repair capacity in response to DNA damage. In support of this hypothesis, Wang et al. (18) noted a trend towards lower levels of chromosome breaks in healthy heavy smokers (>42 pack-years) as compared with never smokers following treatment with bleomycin or benzo(*a*)pyrene diol epoxide, though the association with genotype has not been examined. Lower levels of 8-oxoguanine in lymphocytes of

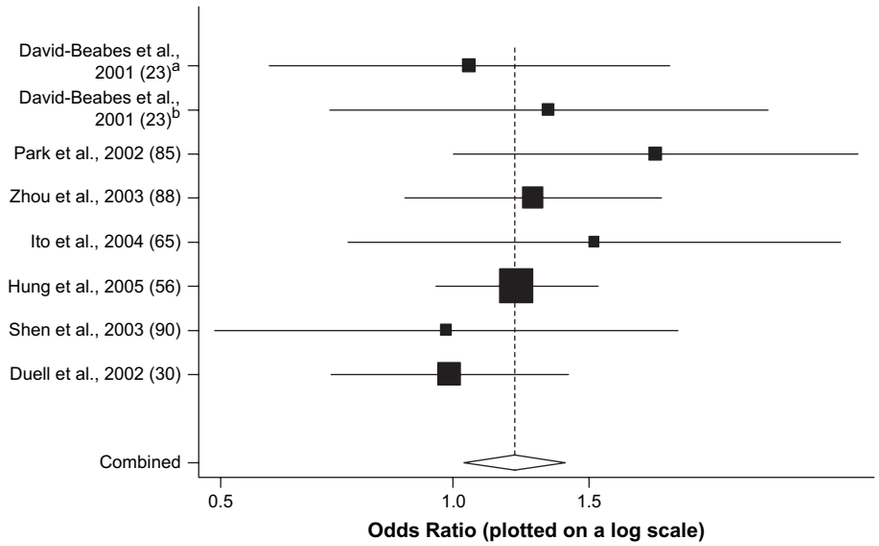

FIGURE 3. Odds ratios for the relation between the x-ray repair cross-complementing group 1 (*XRCC1*) Arg399Gln polymorphism (Arg/Gln and Gln/Gln vs. Arg/Arg) and risk of tobacco-related cancer among light smokers. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the variance of the estimated effect. Diamond, summary odds ratio; horizontal lines, 95% confidence interval. Reference (23)[a] corresponds to the African-American component in the study by David-Beabes et al. (23); reference (23)[b] corresponds to the Caucasian component.

smokers as compared with nonsmokers, which could be explained by the presence of efficient repair processes for the oxidative damage induced by smoking, have also been reported in some studies (45, 46).

There are some limitations inherent in meta-analysis. Each study had different eligibility criteria for subjects and different sources of controls; this should be taken into account when interpreting the summary estimates. For

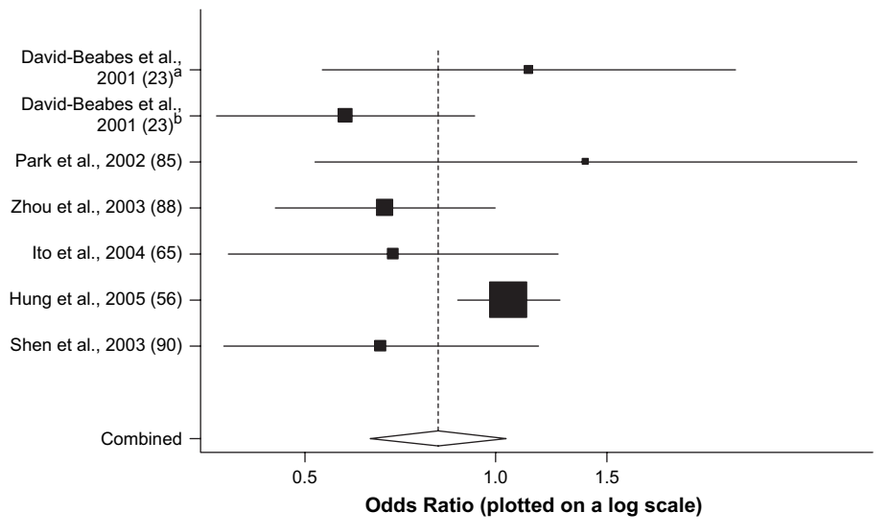

FIGURE 4. Odds ratios for the relation between the x-ray repair cross-complementing group 1 (*XRCC1*) Arg399Gln polymorphism (Arg/Gln and Gln/Gln vs. Arg/Arg) and risk of tobacco-related cancer among heavy smokers. For each study, the odds ratio estimate is plotted with a box; the area of each box is inversely proportional to the variance of the estimated effect. Diamond, summary odds ratio; horizontal lines, 95% confidence interval. Reference (23)[a] corresponds to the African-American component in the study by David-Beabes et al. (23); reference (23)[b] corresponds to the Caucasian component.

example, the effect of *OGG1* Cys/Cys on lung cancer risk was predominantly detected in population-based studies: When studies were stratified by control source, the lung cancer odds ratio for the *OGG1* Cys/Cys genotype was 1.78 (95 percent CI: 1.22, 2.59) using data from population-based studies and 1.09 (95 percent CI: 0.86, 1.31) using data from hospital-based studies. This indicates that the allele distribution of the *OGG1* polymorphism in the hospital control groups might not have been representative of the general population. On the other hand, the effects of the *XRCC1* Arg194Trp polymorphism on tobacco-related cancers from population-based studies (OR = 0.88, 95 percent CI: 0.76, 1.03) and hospital-based studies (OR = 0.82, 95 percent CI: 0.71, 0.94) were comparable. The differences among studies were estimated by tests of heterogeneity and influence analysis, and only the summary estimates without significant heterogeneity at the 0.05 level were considered valid, although the standard test of heterogeneity generally has low statistical power.

The effect of a single common sequence variant might not be detectable in population association studies, and the combination of multiple sequence variants in the same gene and in genes functioning in the same biochemical pathway might be more important in carcinogenesis. A segregation analysis of breast cancer in United Kingdom families suggested that the residual family clustering in noncarriers of *BRCA 1/2* mutations may be explained by a large number of low-penetrance sequence variants (47, 48). Likewise, another recent segregation analysis suggested a multigenic model for lung cancer susceptibility (49). However, it is difficult to assess the effect of the combination of multiple sequence variants via meta-analysis. A large-scale investigation of the multigenic model of cancer through pooling of individual data would be feasible.

Similarly, although we attempted to evaluate effect modification by age of onset and tobacco smoking, only a few investigators reported such results. In addition, interpretation of the results is limited, since the definition of each stratum varied among studies. Moreover, the cancer sites shown to be related to tobacco smoking were combined (34) to obtain sufficient statistical power for further stratified analysis on smoking. However, the magnitudes of the associations with smoking vary across these cancer sites, and the modification of effects on sequence variants might also differ. A more appropriate investigation requires the pooling of individual data; such a coordinated effort can be achieved via collaborative arrangements such as consortia.

Consortia that may be able to undertake pooled analysis have been created for lung cancer (e.g., the International Lung Cancer Consortium (ILCCO)) and head and neck cancer (e.g., the International Head and Neck Cancer Epidemiology Consortium (INHANCE)). Their aims are to increase statistical power to detect low-risk genetic variants and gene-environment interactions and to focus on special subgroups such as early-onset cases, nonsmokers, or patients with tumors of rare histology. Consortia also provide an opportunity for researchers in the field to rapidly test the repeatability of results, as well as discuss markers that may be most relevant for a specific cancer site. With regard to genetic association studies, consortia and international collaborations may be a way to maximize study efficiency and overcome the limitations of individual studies.

ACKNOWLEDGMENTS

This study was funded by a National Cancer Institute R01 grant (contract CA 092039-01A2), a National Cancer Institute R03 grant (contract CA 119704-01), and an Association for International Cancer Research grant (contract 03-281). Dr. Rayjean Hung worked on this study under the tenure of Special Training Awards from the International Agency for Research on Cancer.

Conflict of interest: none declared.

REFERENCES

1. Krokan HE, Nilsen H, Skorpen F, et al. Base excision repair of DNA in mammalian cells. FEBS Lett 2000;476:73–7.
2. Barnes DE, Lindahl T. Repair and genetic consequences of endogenous DNA base damage in mammalian cells. Annu Rev Genet 2004;38:445–76.
3. Ide H, Kotera M. Human DNA glycosylases involved in the repair of oxidatively damaged DNA. Biol Pharm Bull 2004; 27:480–5.
4. Lindahl T, Wood RD. Quality control by DNA repair. Science 1999;286:1897–905.
5. Lu AL, Li X, Gu Y, et al. Repair of oxidative DNA damage: mechanisms and functions. Cell Biochem Biophys 2001;35: 141–70.
6. Spitz MR, Wei Q, Dong Q, et al. Genetic susceptibility to lung cancer: the role of DNA damage and repair. Cancer Epidemiol Biomarkers Prev 2003;12:689–98.
7. Shinmura K, Yokota J. The *OGG1* gene encodes a repair enzyme for oxidatively damaged DNA and is involved in human carcinogenesis. Antioxid Redox Signal 2001;3:597–609.
8. Kohno T, Shinmura K, Tosaka M, et al. Genetic polymorphisms and alternative splicing of the *hOGG1* gene, that is involved in the repair of 8-hydroxyguanine in damaged DNA. Oncogene 1998;16:3219–25.
9. Weiss JM, Goode EL, Ladiges WC, et al. Polymorphic variation in *hOGG1* and risk of cancer: a review of the functional and epidemiologic literature. Mol Carcinog 2005;42:127–41.
10. Janssen K, Schlink K, Gotte W, et al. DNA repair activity of 8-oxoguanine DNA glycosylase 1 (OGG1) in human lymphocytes is not dependent on genetic polymorphism Ser326/ Cys326. Mutat Res 2001;486:207–16.
11. Dherin C, Radicella JP, Dizdaroglu M, et al. Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1 (Ser326Cys) protein which is frequently found in human populations. Nucleic Acids Res 1999;27:4001–7.
12. Dianov GL, Sleeth KM, Dianova II, et al. Repair of abasic sites in DNA. Mutat Res 2003;531:157–63.
13. Izumi T, Hazra TK, Boldogh I, et al. Requirement for human AP endonuclease 1 for repair of 3′-blocking damage at DNA single-strand breaks induced by reactive oxygen species. Carcinogenesis 2000;21:1329–34.
14. Hu JJ, Smith TR, Miller MS, et al. Amino acid substitution variants of *APE1* and *XRCC1* genes associated with ionizing radiation sensitivity. Carcinogenesis 2001;22:917–22.

15. Cappelli E, Taylor R, Cevasco M, et al. Involvement of *XRCC1* and DNA ligase III gene products in DNA base excision repair. J Biol Chem 1997;272:23970–5.
16. Fan J, Otterlei M, Wong HK, et al. XRCC1 co-localizes and physically interacts with PCNA. Nucleic Acids Res 2004; 32:2193–201.
17. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:1513–30.
18. Wang Y, Spitz MR, Zhu Y, et al. From genotype to phenotype: correlating *XRCC1* polymorphisms with mutagen sensitivity. DNA Repair (Amst) 2003;2:901–8.
19. Tuimala J, Szekely G, Gundy S, et al. Genetic polymorphisms of DNA repair and xenobiotic-metabolizing enzymes: role in mutagen sensitivity. Carcinogenesis 2002;23:1003–8.
20. Lunn RM, Langlois RG, Hsieh LL, et al. *XRCC1* polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. Cancer Res 1999;59:2557–61.
21. Matullo G, Palli D, Peluso M, et al. *XRCC1*, *XRCC3*, *XPD* gene polymorphisms, smoking and (32)P-DNA adducts in a sample of healthy subjects. Carcinogenesis 2001;22: 1437–45.
22. Palli D, Russo A, Masala G, et al. DNA adduct levels and DNA repair polymorphisms in traffic-exposed workers and a general population sample. Int J Cancer 2001;94:121–7.
23. David-Beabes GL, London SJ. Genetic polymorphism of *XRCC1* and lung cancer risk among African-Americans and Caucasians. Lung Cancer 2001;34:333–9.
24. Duell EJ, Millikan RC, Pittman GS, et al. Polymorphisms in the DNA repair gene *XRCC1* and breast cancer. Cancer Epidemiol Biomarkers Prev 2001;10:217–22.
25. Hanaoka T, Sugimura H, Nagura K, et al. *hOGG1* exon 7 polymorphism and gastric cancer in case-control studies of Japanese Brazilians and non-Japanese Brazilians. Cancer Lett 2001;170:53–61.
26. Takezaki T, Gao CM, Wu JZ, et al. *hOGG1* Ser(326)Cys polymorphism and modification by environmental factors of stomach cancer risk in Chinese. Int J Cancer 2002;99:624–7.
27. Seedhouse C, Bainton R, Lewis M, et al. The genotype distribution of the *XRCC1* gene indicates a role for base excision repair in the development of therapy-related acute myeloblastic leukemia. Blood 2002;100:3761–6.
28. Stern MC, Umbach DM, van Gils CH, et al. DNA repair gene *XRCC1* polymorphisms, smoking, and bladder cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:125–31.
29. Kelsey KT, Park S, Nelson HH, et al. A population-based case-control study of the *XRCC1* Arg399Gln polymorphism and susceptibility to bladder cancer. Cancer Epidemiol Biomarkers Prev 2004;13:1337–41.
30. Duell EJ, Holly EA, Bracci PM, et al. A population-based study of the Arg399Gln polymorphism in x-ray repair cross-complementing group 1 (*XRCC1*) and risk of pancreatic adenocarcinoma. Cancer Res 2002;62:4630–6.
31. Winsey SL, Haldar NA, Marsh HP, et al. A variant within the DNA repair gene *XRCC3* is associated with the development of melanoma skin cancer. Cancer Res 2000;60:5612–16.
32. Kim SU, Park SK, Yoo KY, et al. *XRCC1* genetic polymorphism and breast cancer risk. Pharmacogenetics 2002;12: 335–8.
33. Shu XO, Cai Q, Gao YT, et al. A population-based case-control study of the Arg399Gln polymorphism in DNA repair gene *XRCC1* and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2003;12:1462–7.
34. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004;83: 1–1438.
35. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
36. Egger M, Davey SG, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
37. Park J, Chen L, Tockman MS, et al. The human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) DNA repair enzyme and its association with lung cancer risk. Pharmacogenetics 2004; 14:103–9.
38. Elahi A, Zheng Z, Park J, et al. The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis 2002;23:1229–34.
39. Xing DY, Tan W, Song N, et al. Ser326Cys polymorphism in *hOGG1* gene and risk of esophageal cancer in a Chinese population. Int J Cancer 2001;95:140–3.
40. Chacko P, Rajan B, Joseph T, et al. Polymorphisms in DNA repair gene *XRCC1* and increased genetic susceptibility to breast cancer. Breast Cancer Res Treat 2005;89:15–21.
41. Yu HP, Zhang XY, Wang XL, et al. DNA repair gene *XRCC1* polymorphisms, smoking, and esophageal cancer risk. Cancer Detect Prev 2004;28:194–9.
42. Matullo G, Guarrera S, Carturan S, et al. DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case-control study. Int J Cancer 2001;92: 562–7.
43. Dhenaut A, Boiteux S, Radicella JP. Characterization of the *hOGG1* promoter and its expression during the cell cycle. Mutat Res 2000;461:109–18.
44. Nelson HH, Kelsey KT, Mott LA, et al. The *XRCC1* Arg399Gln polymorphism, sunburn, and non-melanoma skin cancer: evidence of gene-environment interaction. Cancer Res 2002;62:152–5.
45. van Zeeland AA, de Groot AJ, Hall J, et al. 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. Mutat Res 1999;439: 249–57.
46. Nia AB, Van Schooten FJ, Schilderman PA, et al. A multibiomarker approach to study the effects of smoking on oxidative DNA damage and repair and antioxidative defense mechanisms. Carcinogenesis 2001;22:395–401.
47. Antoniou AC, Pharoah PD, McMullan G, et al. Evidence for further breast cancer susceptibility genes in addition to *BRCA1* and *BRCA2* in a population-based study. Genet Epidemiol 2001;21:1–18.
48. Antoniou AC, Pharoah PD, McMullan G, et al. A comprehensive model for familial breast cancer incorporating *BRCA1*, *BRCA2* and other genes. Br J Cancer 2002;86:76–83.
49. Xu H, Spitz MR, Amos CI, et al. Complex segregation analysis reveals a multigene model for lung cancer. Hum Genet 2005; 116:121–7.
50. Sugimura H, Kohno T, Wakai K, et al. *hOGG1* Ser326Cys polymorphism and lung cancer susceptibility. Cancer Epidemiol Biomarkers Prev 1999;8:669–74.
51. Ito H, Hamajima N, Takezaki T, et al. A limited association of *OGG1* Ser326Cys polymorphism for adenocarcinoma of the lung. J Epidemiol 2002;12:258–65.
52. Sunaga N, Kohno T, Yanagitani N, et al. Contribution of the *NQO1* and *GSTT1* polymorphisms to lung adenocarcinoma susceptibility. Cancer Epidemiol Biomarkers Prev 2002;11: 730–8.
53. Lan Q, Mumford JL, Shen M, et al. Oxidative damage-related genes *AKR1C3* and *OGG1* modulate risks for lung cancer due

to exposure to PAH-rich coal combustion emissions. Carcinogenesis 2004;25:2177–81.
54. Le Marchand L, Donlon T, Lum-Jones A, et al. Association of the *hOGG1* Ser326Cys polymorphism with lung cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:409–12.
55. Wikman H, Risch A, Klimek F, et al. *hOGG1* polymorphism and loss of heterozygosity (LOH): significance for lung cancer susceptibility in a Caucasian population. Int J Cancer 2000; 88:932–7.
56. Hung RJ, Brennan P, Canzian F, et al. Large-scale investigation of base excision repair genetic polymorphisms and lung cancer risk in a multicenter study. J Natl Cancer Inst 2005; 97:567–76.
57. Cho EY, Hildesheim A, Chen CJ, et al. Nasopharyngeal carcinoma and genetic polymorphisms of DNA repair enzymes XRCC1 and hOGG1. Cancer Epidemiol Biomarkers Prev 2003;12:1100–4.
58. Hao B, Wang H, Zhou K, et al. Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res 2004;64:4378–84.
59. Zhang Z, Shi Q, Wang LE, et al. No association between *hOGG1* Ser326Cys polymorphism and risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 2004;13:1081–3.
60. Kim JI, Park YJ, Kim KH, et al. *hOGG1* Ser326Cys polymorphism modifies the significance of the environmental risk factor for colon cancer. World J Gastroenterol 2003;9:956–60.
61. Choi JY, Hamajima N, Tajima K, et al. *hOGG1* Ser326Cys polymorphism and breast cancer risk among Asian women. Breast Cancer Res Treat 2003;79:59–62.
62. Vogel U, Nexo BA, Olsen A, et al. No association between *OGG1* Ser326Cys polymorphism and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:170–1.
63. Xu J, Zheng SL, Turner A, et al. Associations between *hOGG1* sequence variants and prostate cancer susceptibility. Cancer Res 2002;62:2253–7.
64. Vogel U, Olsen A, Wallin H, et al. No association between *OGG1* Ser326Cys and risk of basal cell carcinoma. Cancer Epidemiol Biomarkers Prev 2004;13:1680–1.
65. Ito H, Matsuo K, Hamajima N, et al. Gene-environment interactions between the smoking habit and polymorphisms in the DNA repair genes, *APE1* Asp148Glu and *XRCC1* Arg399Gln, in Japanese lung cancer risk. Carcinogenesis 2004;25:1395–401.
66. Misra RR, Ratnasinghe D, Tangrea JA, et al. Polymorphisms in the DNA repair genes *XPD*, *XRCC1*, *XRCC3*, and *APE/ref-1*, and the risk of lung cancer among male smokers in Finland. Cancer Lett 2003;191:171–8.
67. Popanda O, Schattenberg T, Phong CT, et al. Specific combinations of DNA repair gene variants and increased risk for non-small cell lung cancer. Carcinogenesis 2004; 25:2433–41.
68. Ratnasinghe D, Yao SX, Tangrea JA, et al. Polymorphisms of the DNA repair gene *XRCC1* and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:119–23.
69. Chen S, Tang D, Xue K, et al. DNA repair gene *XRCC1* and *XPD* polymorphisms and risk of lung cancer in a Chinese population. Carcinogenesis 2002;23:1321–5.
70. Lee JM, Lee YC, Yang SY, et al. Genetic polymorphisms of *XRCC1* and risk of the esophageal cancer. Int J Cancer 2001; 95:240–6.
71. Xing D, Qi J, Miao X, et al. Polymorphisms of DNA repair genes *XRCC1* and *XPD* and their associations with risk of esophageal squamous cell carcinoma in a Chinese population. Int J Cancer 2002;100:600–5.
72. Sturgis EM, Castillo EJ, Li L, et al. Polymorphisms of DNA repair gene *XRCC1* in squamous cell carcinoma of the head and neck. Carcinogenesis 1999;20:2125–9.
73. Olshan AF, Watson MA, Weissler MC, et al. *XRCC1* polymorphisms and head and neck cancer. Cancer Lett 2002;178: 181–6.
74. Varzim G, Monteiro E, Silva RA, et al. *CYP1A1* and *XRCC1* gene polymorphisms in SCC of the larynx. Eur J Cancer Prev 2003;12:495–9.
75. Abdel-Rahman SZ, Soliman AS, Bondy ML, et al. Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene *XRCC1* are associated with increased risk of early-onset colorectal carcinoma in Egypt. Cancer Lett 2000;159:79–86.
76. Shen H, Xu Y, Qian Y, et al. Polymorphisms of the DNA repair gene *XRCC1* and risk of gastric cancer in a Chinese population. Int J Cancer 2000;88:601–6.
77. Lee SG, Kim B, Choi J, et al. Genetic polymorphisms of *XRCC1* and risk of gastric cancer. Cancer Lett 2002;187: 53–60.
78. van Gils CH, Bostick RM, Stern MC, et al. Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: an example of polymorphisms in the *XRCC1* gene. Cancer Epidemiol Biomarkers Prev 2002;11:1279–84.
79. Han J, Hankinson SE, De VI, et al. A prospective study of *XRCC1* haplotypes and their interaction with plasma carotenoids on breast cancer risk. Cancer Res 2003;63:8536–41.
80. Smith TR, Miller MS, Lohman K, et al. Polymorphisms of *XRCC1* and *XRCC3* genes and susceptibility to breast cancer. Cancer Lett 2003;190:183–90.
81. Smith TR, Levine EA, Perrier ND, et al. DNA-repair genetic polymorphisms and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:1200–4.
82. Moullan N, Cox DG, Angele S, et al. Polymorphisms in the DNA repair gene *XRCC1*, breast cancer risk, and response to radiotherapy. Cancer Epidemiol Biomarkers Prev 2003;12: 1168–74.
83. Forsti A, Angelini S, Festa F, et al. Single nucleotide polymorphisms in breast cancer. Oncol Rep 2004;11:917–22.
84. Deligezer U, Dalay N. Association of the *XRCC1* gene polymorphisms with cancer risk in Turkish breast cancer patients. Exp Mol Med 2004;36:572–5.
85. Park JY, Lee SY, Jeon HS, et al. Polymorphism of the DNA repair gene *XRCC1* and risk of primary lung cancer. Cancer Epidemiol Biomarkers Prev 2002;11:23–7.
86. Zhang X, Miao X, Liang G, et al. Polymorphisms in DNA base excision repair genes *ADPRT* and *XRCC1* and risk of lung cancer. Cancer Res 2005;65:722–6.
87. Divine KK, Gilliland FD, Crowell RE, et al. The *XRCC1* 399 glutamine allele is a risk factor for adenocarcinoma of the lung. Mutat Res 2001;461:273–8.
88. Zhou W, Liu G, Miller DP, et al. Polymorphisms in the DNA repair genes *XRCC1* and *ERCC2*, smoking, and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2003;12:359–65.
89. Harms C, Salama SA, Sierra-Torres CH, et al. Polymorphisms in DNA repair genes, chromosome aberrations, and lung cancer. Environ Mol Mutagen 2004;44:74–82.
90. Shen M, Hung RJ, Brennan P, et al. Polymorphisms of the DNA repair genes *XRCC1*, *XRCC3*, *XPD*, interaction with environmental exposures, and bladder cancer risk in a case-control study in northern Italy. Cancer Epidemiol Biomarkers Prev 2003;12:1234–40.

91. Sanyal S, Festa F, Sakano S, et al. Polymorphisms in DNA repair and metabolic genes in bladder cancer. Carcinogenesis 2004;25:729–34.
92. Yeh CC, Sung FC, Tang R, et al. Polymorphisms of the *XRCC1*, *XRCC3*, & *XPD* genes, and colorectal cancer risk: a case-control study in Taiwan. BMC Cancer 2005;5:12. (Electronic article).
93. Yu MW, Yang SY, Pan IJ, et al. Polymorphisms in *XRCC1* and glutathione *S*-transferase genes and hepatitis B-related hepatocellular carcinoma. J Natl Cancer Inst 2003;95: 1485–8.
94. Rybicki BA, Conti DV, Moreira A, et al. DNA repair gene *XRCC1* and *XPD* polymorphisms and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 2004;13:23–9.
95. Matsuo K, Hamajima N, Suzuki R, et al. Lack of association between DNA base excision repair gene *XRCC1* Gln399Arg polymorphism and risk of malignant lymphoma in Japan. Cancer Genet Cytogenet 2004;149:77–80.
96. Nelson HH, Kelsey KT, Mott LA, et al. The *XRCC1* Arg399Gln polymorphism, sunburn, and non-melanoma skin cancer: evidence of gene-environment interaction. Cancer Res 2002; 62:152–5.
97. Yin J, Rockenbauer E, Hedayati M, et al. Multiple single nucleotide polymorphisms on human chromosome 19q13.2–3 associate with risk of basal cell carcinoma. Cancer Epidemiol Biomarkers Prev 2002;11:1449–53.

APPENDIX

Internet Sites

Ensembl genome browser: http://www.ensembl.org
GeneCards: http://bioinfo.weizmann.ac.il/cards/index.shtml
Database of Single Nucleotide Polymorphisms: http://www.ncbi.nlm.nih.gov/projects/SNP/